

BIENNIAL
REPORT ON
CARCINOGENS

A Work in Progress

You can't please all of the people all of the time. Never does this adage hold more true, perhaps, than in the case of determining which agents in our environment are probable carcinogens. In the ongoing process of reviewing and revising the criteria for listing such chemicals in the *Biennial Report on Carcinogens*, however, the NIEHS has followed a policy of open, public meetings and solicitation of scientific opinions from all the stakeholders in the hope of capturing the majority opinion. According to George Lucier, director of the Environmental Toxicology Program at the NIEHS, the latest version of the criteria may have accomplished that goal.

The *Biennial Report on Carcinogens* is mandated by the Public Health Service Act, which states that the secretary of the Department of Health and Human Services shall publish a report containing a list of all substances "which are either known to be human carcinogens or may reasonably be anticipated to be human carcinogens; and to which a significant number of persons residing in the United States are exposed." The process of preparing the report, which is carried out by the National Toxicology Program, has in recent years been the subject of controversy between government, industry, public interest

groups, and others who disagreed about both the process itself and the outcome of listing for particular chemicals. In 1994, one particular controversy, surrounding whether glass wool should be listed as a substance reasonably anticipated to be a human carcinogen, refocused attention on the listing issue and prompted officials at the NIEHS and DHHS to direct a review of the listing process and possible revision of the criteria.

Process

In an atmosphere of criticism of government agencies for making behind-the-scenes scientific and regulatory decisions, officials at the NIEHS began the review process with the intention of fostering public discourse on the subject open to all organizations and individuals with an interest or stake in the outcome. To this end, an ad hoc working group of the NTP Board of Scientific Counselors, a primarily non-government group that reviews the scientific activities of the NTP, was formed to

receive public comments on the criteria and review and make recommendations for revising the listing process.

Members of this working group were made up of representatives from academia, industry, labor, public interest groups, state and local health departments, international experts in carcinogenesis, members of the NTP Executive Committee, and NIEHS staff. On 24–25 April 1995, at a public meeting in Washington, DC, the group set about its task of examining the existing process and criteria and determining if changes were needed, and, if so what should be done.

Kenneth Olden, director of the NIEHS and the NTP, chaired the ad hoc working group in the first plenary session of the meeting with addressing the adequacy of existing criteria for listing substances and with deciding whether to incorporate mechanistic data into these criteria. The criteria may include the consideration of sensitive subpopulations or procedures to evaluate the results of animal bioassays or epidemiology studies. The second plenary session was devoted to presentation of public comments concerning the criteria. Comments were presented by representatives from such varied groups as the Chlorobenzene Producers



Association, the United Auto Workers, and the Center for Science in the Public Interest. Following the public comments, participants met in breakout sessions and then reconvened in the third plenary session to report on their deliberations and recommendations.

There was a consensus among the working group that the current criteria for listing substances in the *Biennial Report on Carcinogens* should be revised, although proposals ranged from slight revisions to more substantive changes. Although many recommendations were made, most members of the working group felt that mechanistic data should be used in the selection process. It was also decided that formal guidelines for de-listing chemicals should be incorporated into the biennial report.

Revisions

Based on the recommendations of the ad hoc working group, Lucier and William Jameson at the NIEHS developed revised criteria for review by the NTP's Board of Scientific Counselors. Upon review of the proposed revisions at a meeting June 29, the board passed several resolutions regarding the *Biennial Report on Carcinogens*: mechanistic information should be used in the selection process; the current criteria should be revised; the number of categories should remain at two; revised criteria should include a change in the wording of the categories; an explanatory paragraph regarding the basis of the categories should precede the criteria; and a formal mechanism for de-listing substances should be instituted.

The results of these resolutions are included in the proposed revised criteria as follows: Conclusions regarding carcinogenicity in humans or experimental animals will be based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects or other data relating to mechanism of action, and/or factors that may be unique to a given substance. For the purpose of the *Biennial Report on Carcinogens*, the degrees of evidence are as follows:

1. Known to be Human Carcinogens:

There is sufficient evidence of carcinogenicity from studies in humans that indicates a causal relationship between the agent, substance, or mixture and human cancer.

2. Reasonably Anticipated to be Human Carcinogens:

- There is limited evidence of carcinogenicity from studies in humans which indicate that causal interpretation is credible but that alternative explanations such as chance, bias, or confounding could not adequately be excluded, or

- There is sufficient evidence of carcinogenicity from studies in experimental animals that indicates there is an increased incidence of malignant and/or combined benign and malignant tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor or age at onset.

These recommendations must be reviewed by the NTP Executive Committee, which is made up of heads of agencies or their designates with an interest in NTP activities such as the CDC, NCI, FDA, and other DHHS officials. Upon approval by this committee, final proposed revisions will be submitted to DHHS Secretary Donna Shalala for approval. Submission to Shalala is expected by the end of 1995.

Commentary

Though not everyone may be completely satisfied with the proposed revisions, certainly everyone would agree that the revision with the most impact is the consideration of mechanistic data in the scientific review process preceding formal listing of a chemical. Lucier says that the addition of such information is important because "it allows us to better compare rodent and human responses, which will enable better and more accurate listings of chemicals reasonably anticipated to be carcinogens. Mechanistic data will allow us to strengthen the scientific basis for listings, and in some cases, chemicals could be listed primarily on the presence of convincing mechanistic data that the chemical is likely to cause cancer in humans."

Addition of such information may also address the concerns of groups who question the validity of using animal bioassays as the primary basis for extrapolating human risk, although Lucier stresses, "the *Biennial Report on Carcinogens* is only one part of hazard identification, the first step in the process of risk assessment which spurs regulatory action for chemicals or classes of chemicals." According to Lucier, some chemicals may be listed as a result of using mechanistic data and some may be de-listed. In the long run, the numbers may work out to be much the same. Still, the process of using mechanistic data in addition to existing human and animal data on toxicity is not just a scien-

tific exercise. Bringing the weight of scientific evidence to bear on the problems of protecting human health from exposure to carcinogens hits at the heart of Congress's intent in creating the *Biennial Report on Carcinogens*: "to disseminate prudent information which will prevent human cancer through helping people to take prudent steps to reduce exposure."

Kimberly G. Thigpen

SUSCEPTIBILITY AND RISK ASSESSMENT

The Third Annual Symposium of the Health Effects Research Laboratory

The Health Effects Research Laboratory of the U.S. Environmental Protection Agency is pleased to announce that its Third Annual Symposium will be held November 6-9, 1995 at the North Raleigh Hilton in Raleigh, North Carolina. This third in the Annual HERL Symposium Series on Research Advances in Health Risk Assessment will focus on known factors affecting the susceptibility of humans, experimental animal models, or cell tests systems to environmental toxicants with the goal of refining risk assessment strategies which must consider variable population response. Protection of the "susceptible individual" is a fundamental goal of environmental regulation. Indeed, it is generally accepted that if the susceptible individual is protected, then the entire population will be protected. The format of the HERL Symposium will include invited platform presentations and contributed poster presentations. For more information, please contact:

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